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FILE 'HOME' ENTERED AT 16:00:44 ON 04 SEP 2003

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
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FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 16:01:09 ON 04 SEP 2003

FILE 'EMBASE' ENTERED AT 16:01:09 ON 04 SEP 2003

FILE 'BIOSIS' ENTERED AT 16:01:09 ON 04 SEP 2003

FILE 'BIOTECHDS' ENTERED AT 16:01:09 ON 04 SEP 2003

FILE 'SCISEARCH' ENTERED AT 16:01:09 ON 04 SEP 2003

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FILE 'LIFESCI' ENTERED AT 16:01:09 ON 04 SEP 2003


```
=> s "ldl receptor?"
L1       22565 "LDL RECEPTOR?"

=> s "low density lipoprotein receptor?"
L2       17489 "LOW DENSITY LIPOPROTEIN RECEPTOR?"

=> s l1 or l2
L3       31755 L1 OR L2

=> s mapk
L4       42715 MAPK

=> s l3 and l4
L5          99 L3 AND L4

=> s p42(2w)44
```

L6 2221 P42(2W) 44

=> s l5 and l6
L7 35 L5 AND L6

=> s l5 and l7
L8 35 L5 AND L7

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 15 DUP REM L8 (20 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L9 ANSWER 1 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2003:633436 SCISEARCH
THE GENUINE ARTICLE: 701YF
TITLE: LDL immune complexes stimulate **LDL receptor** expression in U937 histiocytes via extracellular signal-regulated kinase and AP-1
AUTHOR: Fu Y C; Huang Y; Bandyopadhyay S; Virella G; Lopes-Virella M F (Reprint)
CORPORATE SOURCE: Raplh H Johnson Vet Adm Med Ctr, Charleston, SC 29401 USA (Reprint); Med Univ S Carolina, Div Endocrinol Diabet & Med Genet, Dept Med, Charleston, SC 29425 USA; Med Univ S Carolina, Dept Immunol & Microbiol, Charleston, SC 29425 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF LIPID RESEARCH, (JUL 2003) Vol. 44, No. 7, pp. 1315-1321.
Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0022-2275.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 21
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have previously shown that LDL-containing immune complexes (LDL-ICs) induce up-regulation of **LDL receptor** (LDLR) expression in human macrophages. The present study further investigated the molecular mechanisms leading to LDLR up-regulation by LDI-ICs as well as the signaling pathways involved. Results showed that treatment of U937 histiocytes with LDL-ICs did not increase the precursors and the cleaved forms of sterol-regulatory element binding proteins (SREBPs) la and 2, suggesting that SREBPs may not be involved in LDLR up-regulation by LDIrICs. Promoter deletion and mutation studies showed that the AP-1 binding sites were essential for LDL-IC-stimulated LDLR expression. Electrophoretic mobility shift assays further demonstrated that LDL-ICs stimulated transcription factor AP-1 activity. Studies assessing the signaling pathways involved in LDLR up-regulation by LDL-ICs showed that the up-regulation of LDLR was extracellular signal-regulated kinase (ERK) dependent. In conclusion, the present study shows that LDL ICs up-regulate LDLR expression via the ERK signaling pathway and the AP-1 motif-dependent transcriptional activation.

L9 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
ACCESSION NUMBER: 2003:191240 BIOSIS
DOCUMENT NUMBER: PREV200300191240
TITLE: pp90RSK- and protein kinase C-dependent pathway regulates p42/44MAPK-induced **LDL receptor** transcription in HepG2 cells.

AUTHOR(S): Kapoor, Gurpreet S.; Golden, Carmen; Atkins, Brett; Mehta, Kamal D. (1)
CORPORATE SOURCE: (1) Department of Molecular and Cellular Biochemistry, College of Medicine and Public Health, Ohio State University, 1645 Neil Ave., 464 Hamilton Hall, Columbus, OH, 43210, USA: mehta.80@osu.edu USA
SOURCE: Journal of Lipid Research, (March 2003, 2003) Vol. 44, No. 3, pp. 584-593. print.
ISSN: 0022-2275.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We have previously shown that different extracellular stimuli require signaling through the Raf/MEK/p42/44MAPK cascade to induce **LDL receptor** expression. The present studies were designed to delineate the molecular mechanisms underlying p42/44MAPK-induced **LDL receptor** transcription in HepG2-DELTARaf-1:ER cells, a modified HepG2 cell line in which the Raf-1/MEK/p42/44MAPK cascade can be specifically activated by anti-estradiol ICI182,780 in an agonist-specific manner. Using these cells, we show that: a) **LDL receptor** induction was reduced in reporter constructs containing mutation in either Sp1 or sterol-regulatory element-1 (SRE-1) sites, whereas inactivation of both sites abolished the induction; b) E1A, which inhibits CREB binding protein (CBP), a common activator of SRE-1 binding protein and Sp1, strongly repressed the induction; c) intracellular inhibition of the 90 kDa ribosomal S6 kinase (pp90RSK) cascade reduced **LDL receptor** induction; d) highly selective protein kinase C (PKC) inhibitors effectively abrogated the induction without affecting activation of pp90RSK; and e) overexpression of PKCbeta significantly induced **LDL receptor** promoter activity. Taken together, these results demonstrate that pp90RSK and PKCbeta are downstream effectors and Sp1, SRE-1 binding protein, and CBP are part of the transcriptional complex resulting in induction of **LDL receptor** expression in response to activation of the Raf/MEK/p42/44MAPK cascade. These findings identify for the first time a role for PKCbeta in determining the specificity of p42/44MAPK signaling by participating with pp90RSK in regulating gene expression.

L9 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003045828 MEDLINE
DOCUMENT NUMBER: 22392857 PubMed ID: 12504834
TITLE: Oxidized-LDL through LOX-1 increases the expression of angiotensin converting enzyme in human coronary artery endothelial cells.
AUTHOR: Li Dayuan; Singh Robin M; Liu Ling; Chen Hongjiang; Singh Balkrishna M; Kazzaz Nelly; Mehta Jawahar L
CORPORATE SOURCE: Department of Internal Medicine, University of Arkansas for Medical Sciences, Mail Slot 532, 4301 W Markham, Little Rock, AR 72205, USA.
SOURCE: CARDIOVASCULAR RESEARCH, (2003 Jan) 57 (1) 238-43.
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030131
Last Updated on STN: 20030430
Entered Medline: 20030429

AB BACKGROUND AND OBJECTIVES: Our previous studies have shown that oxidized low-density lipoprotein (ox-LDL) and angiotensin II (Ang II) influence each other's action in endothelial cells. This study was designed to examine the regulation by ox-LDL of the expression of angiotensin

converting enzyme (ACE) gene in human coronary artery endothelial cells (HCAECs). In addition, we studied the effect of the HMG CoA reductase inhibitor simvastatin on this interaction. METHODS AND RESULTS: Cultured HCAECs were incubated with ox-LDL (10-80 microg/ml) for 1-24 h. Ox-LDL increased the expression of ACE in a concentration- and time-dependent fashion. The upregulation of ACE expression in response to ox-LDL was mediated by its endothelial receptor LOX-1, since pretreatment of HCAECs with a blocking antibody to LOX-1 prevented the expression of ACE ($P<0.01$). Native-LDL had no significant effect on ACE expression. In this process, ox-LDL-induced activation of mitogen-activated protein kinase (**MAPK p42/44**) played an important role, since pretreatment of HCAECs with the **MAPK p42/44** inhibitor (PD98059, 10 microM) inhibited **MAPK** activation and subsequently attenuated the expression of ACE ($P<0.01$ vs. ox-LDL alone). In other experiments, we pretreated HCAECs with simvastatin (10 microM) and then exposed the cells to ox-LDL. Simvastatin markedly attenuated ox-LDL-induced **MAPK** activation, and concurrently reduced ACE expression ($P<0.01$ vs. ox-LDL alone). CONCLUSIONS: Our observations provide direct evidence that ox-LDL via LOX-1 activation induces ACE gene expression in HCAECs, and **MAPK** activation plays a signal transduction role in this process. Simvastatin, which inhibits **MAPK** activation, also blocks ox-LDL-mediated upregulation of ACE.

L9 ANSWER 4 OF 15 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002270304 MEDLINE
DOCUMENT NUMBER: 21993139 PubMed ID: 11997513
TITLE: Critical role of diacylglycerol- and phospholipid-regulated protein kinase C epsilon in induction of **low-density lipoprotein receptor** transcription in response to depletion of cholesterol.
AUTHOR: Mehta Kamal D; Radominska-Pandya Anna; Kapoor Gurpreet S; Dave Bhuvanesh; Atkins Brett A
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus, Ohio 43210, USA.. mehta.80@osu.edu
CONTRACT NUMBER: DK56226 (NIDDK)
R01 HL67760 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Jun) 22 (11) 3783-93. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020611
Entered Medline: 20020606

AB Induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to depletion of cellular sterols in animal cells is well established. The intracellular signal or signals involved in regulating this process, however, remain unknown. Using a specific inhibitor of protein kinase C (PKC), calphostin C, we show the requirement of this kinase in the induction process in human hepatoma HepG2 cells. Overexpression of PKC epsilon, but not PKC alpha, -gamma, -delta, or -zeta was found to dramatically induce (approximately 18-fold) **LDL receptor** promoter activity. Interestingly, PKC epsilon-mediated induction was found to be sterol resistant. To further establish that PKC epsilon is involved in the sterol regulation of **LDL receptor** gene transcription, endogenous PKC epsilon was specifically inhibited by transfection with antisense PKC epsilon phosphorothionate oligonucleotides. Antisense treatment decreased

endogenous PKC epsilon protein levels and completely blocked induction of **LDL receptor** transcription following sterol depletion. PKC epsilon-induced **LDL receptor** transcription is independent of the extracellular signal-regulated kinase 1 and 2 (**p42/44(MAPK)**) cascade, because the MEK-1/2 inhibitor, PD98059 did not inhibit, even though it blocked **p42/44(MAPK)** activation. Finally, photoaffinity labeling studies showed an isoform-specific interaction between PKC epsilon and sterols, suggesting that sterols may directly modulate its function by hampering binding of activators. This was confirmed by PKC activity assays. Altogether, these results define a novel signaling pathway leading to induction of **LDL receptor** transcription following sterol depletion, and a model is proposed to account for a new function for PKC epsilon as part of a sterol-sensitive signal transduction pathway in hepatic cells.

L9 ANSWER 5 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN DUPLICATE 4

ACCESSION NUMBER: 2002274870 EMBASE
TITLE: Role of mitogen-activated protein kinases and protein kinase C in regulating **low-density lipoprotein receptor** expression.
AUTHOR: Mehta K.D.
CORPORATE SOURCE: K.D. Mehta, Department of Cellular Biochemistry, Ohio State Univ. College of Medicine, Columbus, OH 43210, United States. mehta.80@osu.edu
SOURCE: Gene Expression, (2002) 10/4 (153-164).
Refs: 95
ISSN: 1052-2166 CODEN: GEEXEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cell signaling pathways that culminate in induction of low-density lipoprotein (**LDL**) **receptor** transcription in response to a variety of extracellular and intracellular signals are beginning to be defined. Evidence is accumulating that **LDL receptor** transcription is under complex regulation and that a major pathway of induction by cytokines, growth factors, anisomycin, and phorbol esters involves the extracellular/mitogen-activated protein kinase (**p42/44(MAPK)**) cascade. In fact, degree **p42/44(MAPK)** activation determines the extent of **LDL receptor** induction. The suppression of **LDL receptor** expression by stress-activated p38(**MAPK**) via **p42/44(MAPK)** provides a potential mechanism for stress-induced hypercholesterolemia observed in humans and animals. Moreover, endogenous signals such as cholesterol regulate **LDL receptor** transcription through a different signaling cascade involving protein kinase C.epsilon. isoform (PKC.epsilon.). The ability of cholesterol to directly bind PKC.epsilon. in an isoform-specific manner strongly supports its role in sensing the cellular cholesterol levels. The emerging picture from the above studies is that regulation of **LDL receptor** transcription results from the activity of a number of interlinked regulatory molecules and pathways, rather than from a single linear series of events. These studies will provide the necessary framework for understanding differential responses within human populations to atherosclerosis following high-fat/cholesterol diet. This information may also provide new strategies to modulate specific gene expression with the hope to develop novel therapies for the treatment of hypercholesterolemia.

L9 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:186246 BIOSIS
DOCUMENT NUMBER: PREV200300186246
TITLE: Requirement of pp90RSK and protein kinase C in p42/44MAPK-induced **LDL receptor** transcription.
AUTHOR(S): Mehta, K. D. (1); Atkins, B. (1); Kapoor, G. S. (1)
CORPORATE SOURCE: (1) Molecular and Cellular Biochemistry, College of Medicine, Ohio State University, Columbus, OH, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 17a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L9 ANSWER 7 OF 15 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002433781 MEDLINE
DOCUMENT NUMBER: 22177391 PubMed ID: 12190111
TITLE: Activation of Raf-1/MEK-1/2/**p42/44**(**MAPK**) cascade alone is sufficient to uncouple **LDL receptor** expression from cell growth.
AUTHOR: Kapoor Gurpreet S; Atkins Brett A; Mehta Kamal D
CORPORATE SOURCE: Department of Molecular and Cellular Biochemistry, The Ohio State University College of Medicine, Columbus 43210, USA.
CONTRACT NUMBER: R01 HL-65540-01A1 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2002 Jul) 236 (1-2) 13-22.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020823
Last Updated on STN: 20030416
Entered Medline: 20030410

AB Our previous observation that induction of low density lipoprotein (**LDL**) **receptor** expression by a variety of extracellular signals is blocked by PD98059, a specific mitogen-activated protein kinase kinase inhibitor, led to the suggestion that the growth-responsive **p42/44**(**MAPK**) cascade plays a critical role in regulating **LDL receptor** transcription. To analyze the specific contribution of the **p42/44**(**MAPK**) cascade in regulating cell growth and **LDL receptor** induction, we established a HepG2-derived cell line that stably expresses an inducible form of oncogenic human Raf-1 kinase. Using this system, we provide direct evidence that specific activation of this cascade alone is not only required but is sufficient to fully induce **LDL receptor** expression. Interestingly, degree of **p42/44**(**MAPK**) activation determines the extent of **LDL receptor** induction. However, activation of **p42/44**(**MAPK**) in the above cells led to the inhibition of DNA synthesis, caused growth arrest, decrease in cyclin A and upregulation of p21(Cip) expression in a time-dependent manner. These results suggest that each of these two processes can be regulated independently of each other in response to **p42/44**(**MAPK**) activation. Thus, extent of **p42/44**(**MAPK**) activation may be important in transducing divergent cellular responses in human cells with implications for altered signaling resulting in

hypercholesterolemia.

L9 ANSWER 8 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:559059 SCISEARCH
THE GENUINE ARTICLE: 313NH
TITLE: High intensity **p42/44(MAPK)** cascade uncouples **LDL receptor** induction from cell growth.
AUTHOR: Mehta K (Reprint); Kapoor G; Atkins B
CORPORATE SOURCE: UNIV ARKANSAS, COLL MED, LITTLE ROCK, AR 72205
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (11 MAY 2000) Vol. 14, No. 8, pp. 308-308. Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L9 ANSWER 9 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
ACCESSION NUMBER: 2000226341 EMBASE
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression.
AUTHOR: Mehta K.D.; Miller L.
CORPORATE SOURCE: K.D. Mehta, Dept. Biochemistry/Molecular Biology, College of Medicine, University of Arkansas, 4301 West Markham, Little Rock, AR 72205, United States
SOURCE: Trends in Cardiovascular Medicine, (2000) 9/7 (201-205). Refs: 38
ISSN: 1050-1738 CODEN: TCMDEQ
PUBLISHER IDENT.: S 1050-1738(00)00021-9
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have recently shown that different signal transduction pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(**MAPK**) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a new dimension of complexity in the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(**MAPK**) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between **MAPKs** opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. Copyright (C) 1999 Elsevier Science Inc.

L9 ANSWER 10 OF 15 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999321880 MEDLINE

DOCUMENT NUMBER: 99321880 PubMed ID: 10391894
TITLE: One-way cross-talk between p38(**MAPK**) and **p42/44(MAPK)**. Inhibition of p38(**MAPK**) induces **low density lipoprotein receptor** expression through activation of the **p42/44(MAPK**) cascade.
AUTHOR: Singh R P; Dhawan P; Golden C; Kapoor G S; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.
CONTRACT NUMBER: HL-51592 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19593-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20000303
Entered Medline: 19990805

AB In this paper, we report that SB202190 alone, a specific inhibitor of p38(**MAPK**), induces low density lipoprotein (**LDL**) **receptor** expression (6-8-fold) in a sterol-sensitive manner in HepG2 cells. Consistent with this finding, selective activation of the p38(**MAPK**) signaling pathway by expression of MKK6b(E), a constitutive activator of p38(**MAPK**), significantly reduced **LDL receptor** promoter activity. Expression of the p38(**MAPK**) alpha-isoform had a similar effect, whereas expression of the p38(**MAPK**) betaII-isoform had no significant effect on **LDL receptor** promoter activity. SB202190-dependent increase in **LDL receptor** expression was accompanied by induction of **p42/44(MAPK)**, and inhibition of this pathway completely prevented SB202190-induced **LDL receptor** expression, suggesting that p38(**MAPK**) negatively regulates the **p42/44(MAPK)** cascade and the responses mediated by this kinase. Cross-talk between these kinases appears to be one-way because modulation of **p42/44(MAPK)** activity did not affect p38(**MAPK**) activation by a variety of stress inducers. Taken together, these findings reveal a hitherto unrecognized one-way communication that exists between p38(**MAPK**) and **p42/44(MAPK)** and provide the first evidence that through the **p42/44(MAPK)** signaling cascade, the p38(**MAPK**) alpha-isoform negatively regulates **LDL receptor** expression, thus representing a novel mechanism of fine tuning cellular levels of cholesterol in response to a diverse set of environmental cues.

L9 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999438160 MEDLINE
DOCUMENT NUMBER: 99438160 PubMed ID: 10508211
TITLE: Critical role of **p42/44(MAPK)** activation in anisomycin and hepatocyte growth factor-induced **LDL receptor** expression: activation of Raf-1/Mek-1/**p42/44(MAPK**) cascade alone is sufficient to induce **LDL receptor** expression.
AUTHOR: Dhawan P; Bell A; Kumar A; Golden C; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, College of Medicine, University of Arkansas for Medical Sciences,

4301 West Markham, Little Rock, AR 72205, USA.
CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1999 Oct) 40 (10) 1911-9.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991223

AB The protein synthesis inhibitor anisomycin activates stress-related mitogen-activated protein kinases (**MAPKs**), namely, c-jun NH(2)-terminal kinase (p46/54(JNK)) and p38(**MAPK**) in mammalian cells. In this paper, we show that although exposure to anisomycin resulted in rapid and strong activation of p46/54(JNK) and p38(**MAPK**), with a delayed low level dual-phosphorylation of mitogen/extracellular protein kinase (**p42/44**(**MAPK**)), low density lipoprotein (**LDL**) **receptor** induction depends solely on the mild activation of **p42/44**(**MAPK**) signaling cascade in HepG2 cells. Unlike hepatocyte growth factor (HGF) which caused **LDL receptor** induction via rapid, strong, and Ras-dependent **p42/44**(**MAPK**) activation, anisomycin-induced **p42/44**(**MAPK**) activity and increased **LDL receptor** expression in a Ras-independent manner. Finally, we examined the role of the **p42/44**(**MAPK**) signaling cascade in **LDL receptor** induction by activating this kinase independently of anisomycin or HGF. By using estrogen-dependent human Raf-1 protein kinase in transient transfection assays, we show that the exclusive activation of the Raf-1/MEK-1/**p42/44**(**MAPK**) signaling cascade with antiestrogen ICI 182, 780 caused induction of **LDL receptor** expression to the same level as observed with either HGF or anisomycin. Consistent with the role of **p42/44**(**MAPK**), induction was strongly inhibited by pretreatment with the MEK-1/2 inhibitor PD98059.Our observation that anisomycin can use **p42/44**(**MAPK**) signaling cascade is a departure from established thinking, and the results presented shows that activation of the **p42/44**(**MAPK**) alone is sufficient to fully induce **LDL receptor** transcription.

L9 ANSWER 12 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:468792 SCISEARCH
THE GENUINE ARTICLE: 325ZV
TITLE: Inhibition of stress-activated p38 mitogen-activated protein kinase induces **low-density lipoprotein receptor** expression
AUTHOR: Mehta K D (Reprint); Miller L
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, COLL MED, DEPT BIOCHEM & MOL BIOL, SLOT 516, 4301 W MARKHAM, LITTLE ROCK, AR 72205 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN CARDIOVASCULAR MEDICINE, (OCT 1999) Vol. 9, No. 7, pp. 201-205.
Publisher: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
ISSN: 1050-1738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have recently shown that different signal transduction. pathways initiated by a variety of agents converge on growth-responsive **p42/44(MAPK)** signaling cascade to induce low-density lipoprotein (**LDL**) **receptor** expression. Our recent demonstration that stress-activated p38(**MAPK**) negatively regulates **LDL receptor** expression in an isoform-specific manner via modulation of **p42/44(MAPK)** cascade represents a view dimension of complexity in. the molecular communication that governs **LDL receptor** expression. The suggested one-way communication between p38(**MAPK**) and **p42/44(MAPK)** provides a potential mechanism for fine-tuning cellular levels of cholesterol in response to a diverse set of environmental cues, including stress. Cross talk between **MAPKs** opens new avenues toward understanding a variety of pathogenic processes; this makes them tempting targets for therapeutic interventions in cardiovascular diseases. (Trends Cardiovasc Med 1999;9:201-205), (C) 1999, Elsevier Science Inc.

L9 ANSWER 13 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:167257 BIOSIS
DOCUMENT NUMBER: PREV199900167257
TITLE: **LDL receptor** expression is regulated positively by P42/44MAPK pathway in hepatic cells.
AUTHOR(S): Dhawan, P. (1); McMahon, M.; Mehta, K. D. (1)
CORPORATE SOURCE: (1) Dep. Biochemistry Molecular Biology, Univ. Ark. Med. Sciencdes 4301, West Markham St., Littlerock, AR 72205 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A194.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L9 ANSWER 14 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:808341 SCISEARCH
THE GENUINE ARTICLE: 226QW
TITLE: **Ldl receptor** expression is regulated positively by **p42/44(MAPK)** pathway in hepatic cells.
AUTHOR: Dhawan P (Reprint); McMahon M; Mehta K D
CORPORATE SOURCE: UNIV ARKANSAS MED SCI, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72205; UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA 94145
COUNTRY OF AUTHOR: USA
SOURCE: FASEB JOURNAL, (12 MAR 1999) Vol. 13, No. 4, Part 1, Supp. [S], pp. A194-A194.
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L9 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998052315 MEDLINE
DOCUMENT NUMBER: 98052315 PubMed ID: 9392422
TITLE: Phorbol ester-induced **low density lipoprotein receptor** gene expression in

HepG2 cells involves protein kinase C-mediated **p42 /44** MAP kinase activation.

AUTHOR: Kumar A; Chambers T C; Cloud-Heflin B A; Mehta K D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205-7199, USA.

CONTRACT NUMBER: HL-51592-04 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1997 Nov) 38 (11) 2240-8.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
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AB The signaling pathway involved in low density lipoprotein (**LDL**) **receptor** gene expression induced by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated in the human hepatoma HepG2 cell line. Treatment of HepG2 cells with 100 nM TPA resulted in an approximately 20-fold increase in **LDL receptor** mRNA level, as determined by RT-PCR, which peaked at 2-4 h of treatment and subsequently declined. The protein kinase C (PKC) inhibitors calphostin C and staurosporine prevented TPA-mediated **LDL receptor** mRNA induction. In contrast, TPA did not affect squalene synthase mRNA expression. Immunoblotting of cell extracts with isozyme-specific PKC antibodies revealed that HepG2 cells expressed PKC alpha, which was mainly cytosolic, and PKC beta, PK epsilon, and PKC zeta, all of which were present in both the cytosolic and particulate fractions. Treatment of HepG2 cells with 100 nM TPA resulted in translocation of cytosolic PKC alpha to the particulate fraction, with a maximum at 30 min-2 h of treatment, but was without effect on the subcellular distribution of the other isozymes. TPA treatment also led to activation of the mitogen-activated protein kinase (**MAPK**) ERK cascade. The specific **MAPK** pathway inhibitor PD98059 blocked TPA-induced ERK activation. Furthermore, pretreatment of cells with PD98059 inhibited TPA-induced **LDL receptor** mRNA induction. Moreover, pretreatment of cells with calphostin C inhibited TPA-mediated ERK activation and **LDL receptor** mRNA induction in a dose-dependent fashion. Based on a close kinetic correlation between PKC alpha translocation and ERK activation, and the effects of specific inhibitors, these findings suggest that translocation/activation of PKC alpha, and subsequent activation of the Raf-1/MEK/ERK **MAPK** cascade, represent key events in the transcriptional induction of **LDL receptor** gene by TPA in HepG2 cells.

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